

in the characterization of the physical, chemical (other than exhaustive extraction) and mechanical properties of the device should be applicable to the intended use of the device in humans. Infrared measurements of the surface of device components as they occur in the final, sterilized product should be provided.

Biocompatibility testing data must be provided for all materials (pad, cuff, pump, reservoir, tubing, filling agents, gels, lubricants, and any other materials) in the implanted mechanical/hydraulic urinary continence device, including all color additives (ink, dyes, markings, etc.) used to fabricate the implanted mechanical/hydraulic urinary continence device. FDA guidance on biocompatibility testing is available in the document titled "Tripartite Biocompatibility Guidance for Medical Devices." A copy may be obtained upon request from the Division of Small Manufacturers Assistance (HFZ-220), Center for Devices and Radiological Health, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Biocompatibility evaluation should follow the methodology of tests for tissue contacting, long-term internal devices.

Toxicological effects (e.g., cytotoxicity, mutagenicity, effects on the immune system, and reproductive and developmental toxicity) should be identified. Complete mutagenicity testing of extracts from the finished, sterilized components of the device should be provided. These tests should include the following: Bacterial mutagenicity, mammalian mutagenicity, deoxyribonucleic acid (DNA) damage, and cell transformation assay.

Acute, subchronic, and chronic toxicity studies using the chemicals recovered by the above exhaustive extraction processes should be provided in the evaluation of the long-term biocompatibility of the device, including dose response and time to response as well as gross and histopathological findings in tissues both surrounding implants and distal to implant sites (lymph nodes, prostate, urethra, bladder, ovaries/testes, liver, kidneys, lungs, uterus, etc.). Animal studies of carcinogenicity, reproductive toxicity, teratogenicity, and later effects on offspring must be performed using scientifically justified test methods. These studies must include animal testing of the extracts from the final sterilized device. Teratology/reproductive testing of the final sterilized device and extractables should be performed in an appropriate species using validated methods. Furthermore, for those devices that

contain silicone gel, a subset of these studies must test the compounds extracted from the materials of the sterilized device for estrogen-like antigonadotropic activity in an appropriate animal model using scientifically valid methods.

Pharmacokinetic/biodegradation studies of all materials contained in the finished device should state all materials of toxicological concern, such as amine, silicone, and fluorosilicone compounds. Of special concern are questions regarding the ultimate fate, quantities, sites/organs of deposition, routes of excretion, and potential clinical significance of silicone shedding, retention, and migration. Data on the distribution and metabolic fate of amine containing components, silicone, and any other materials used in the manufacturing of the device should be supplied.

Animal testing should also be conducted to study the effect of implantation upon device function and material integrity. Complete device chemical characterization and mechanical testing should be performed after devices have been implanted in an appropriate animal model for an appropriate length of time. Of special concern is the material integrity of the pad, cuff, reservoir, pump, tubing, joints, etc., which should be functionally tested and investigated using electron microscopy. The results of this testing should be compared to the failure rates noted during *in vitro* testing and clinical studies in order to demonstrate that the animal model and study duration chosen are appropriate.

For the implanted mechanical/hydraulic urinary continence device designs that contain silicone gel, or employ a silicone gel as a lubricant, the gel bleed performance of the device, as determined from the results of measurements using a standard diffusion cell maintained at a temperature simulating physiologic conditions using stirred, physiologic saline as a receptacle medium for the bleed, must be reported. Each variation in thickness or device design must be measured to accurately determine diffusion coefficients (with appropriate time dependencies). The chemical identification of the bleed product, including, but not limited to, amine containing components, volatile and nonvolatile silicone cyclics and oligomers below a molecular weight of 1,500 and molecular weight distribution, must be reported.

For the polyurethane covered designs (foam or elastomer), FDA believes that *in vivo* implant studies must be performed to identify and determine the

bioabsorption, distribution, and elimination of the polyurethane covering (as well as their degradation products) in experimental animals. It is also important to identify and determine the mechanism and rate of degradation, as well as the quantity of TDA or other products generated by the breakdown of polyurethane covered implanted mechanical/hydraulic urinary continence devices after prolonged exposure under physical conditions in animals. Additionally, the agency recommends that retrospective epidemiological and prospective clinical studies be designed to assess the potential of cancer and other long-term complications related to implanted mechanical/hydraulic urinary continence devices containing polyurethane. The agency suggests that these preclinical and epidemiological studies be conducted as a separate subset of implanted mechanical/hydraulic urinary continence device safety studies.

*In vitro* testing should be conducted at the component, subassembly, and final device levels and must examine all aspects of device design, construction, and operation. This testing should also demonstrate how the device design and manufacturing processes address the failure mode and effects analysis. The failure mode effects analysis should be provided. Copies of the original data sheets from all tests must be included in the PMA. All device failures must be completely described, and the corrective actions taken to eliminate or minimize further recurrence should also be identified.

An adequate number of samples of each model, based on relevant power calculations, will be required. If marketing approval is sought for multiple device versions, each version requires its own set of preclinical tests and results. If sample devices of each available size are not tested, it must be clearly indicated which device sizes were used for each test. The absence of testing on each size must be justified by analysis demonstrating that the results from the tested devices will accurately predict results for the untested device sizes.

The test conditions and acceptance criteria for all tests should be completely explained and justified. All tests should be performed on final, sterilized devices in an environment simulating the possible range of anticipated *in vivo* conditions (temperatures, pressures, forces, stresses, etc.), where possible. All methods used to determine the condition of the device after testing, e.g., visual examination, electrical